ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2021
Generics

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ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin Guidance for Industry[1]

I. INTRODUCTION

This guidance is intended to assist potential applicants in determining when an application for a synthetic peptide drug product (synthetic peptide) that refers to a previously approved peptide drug product of recombinant deoxyribonucleic acid (rDNA) origin (peptide of rDNA origin) should be submitted as an abbreviated new drug application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) rather than as a new drug application (NDA) under section 505(b) of the FD&C Act.[2] Specifically, this guidance provides recommendations for evaluating whether an ANDA submission is appropriate for a synthetic peptide that references any of the following five previously approved peptide drug products of rDNA origin: glucagon, liraglutide, nesiritide, teriparatide, and teduglutide.[3]

Given the current state of technology for peptide synthesis and characterization, FDA believes it is now possible for an ANDA applicant to demonstrate that the active ingredient in a proposed

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[1] This guidance has been prepared by the Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] This guidance does not address ANDAs for peptides of rDNA origin. Based on the types of data permitted to be submitted in an ANDA (see section 505(j)(2)(A) of the FD&C Act) and current scientific considerations, FDA does not expect that an ANDA could include sufficient evidence (e.g., clinical investigations to assess potential immunogenicity) for approval of a proposed peptide of rDNA origin at this time. An applicant seeking approval of a proposed peptide of rDNA origin may file a 505(b)(2) application or a "stand-alone" NDA submitted under section 505(b)(1) of the FD&C Act.

[3] This guidance does not address all studies and information that should be submitted in support of an ANDA for a synthetic peptide. Applicants should check on the availability of other guidances, including product-specific guidances, for such recommendations. Guidances relating to generic drugs can be found at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs. Product-specific guidances for generic drug development can be found athttps://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development. Also, a potential applicant may request information on a specific element of generic drug development via controlled correspondence or, for complex products such as peptides, may submit a request for a Pre-ANDA meeting.

generic synthetic peptide drug product (proposed generic synthetic peptide) is the "same" as the active ingredient in a previously approved peptide of rDNA origin. For a synthetic peptide that is intended to be a "duplicate"[4] of a previously approved peptide of rDNA origin, a determination of whether an application for the synthetic peptide should be submitted as an ANDA depends largely on its impurity profile as compared to the impurity profile for the peptide of rDNA origin. Differences in impurities, particularly peptide-related impurities, may affect the safety or effectiveness of a peptide drug product as compared to the RLD.

Submission of an ANDA for a proposed generic synthetic peptide for which the reference listed drug (RLD) is a peptide of rDNA origin generally would be appropriate if, among other things, the applicant can: 1) show that, for each peptide-related impurity that is found in both the proposed generic synthetic peptide and the RLD, the level of such impurity in the proposed generic synthetic peptide is the same as or lower than that found in the RLD; 2) show that the proposed generic synthetic peptide does not contain any new specified peptide-related impurity that is more than 0.5 percent of the drug substance;[5] 3) characterize each new specified peptide-related impurity; and 4) justify for each new specified peptide-related impurity that is no more than 0.5 percent of the drug substance why the presence of such impurity would not be expected to affect the safety or effectiveness of the proposed generic synthetic peptide as compared to that of the RLD.[6] This information will enable FDA to evaluate the purity of the proposed generic synthetic peptide and to confirm that it and the RLD of rDNA origin can be expected to have the same safety profile (including with respect to the risk of immunogenicity due to peptide-related impurities) when administered to patients under the conditions specified in the labeling.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

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[4] The term "duplicate" generally refers to a drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug. See the proposed rule entitled "Abbreviated New Drug Application Regulations" (54 FR 28872 at 28877, July 10, 1989).

[5] A new specified peptide-related impurity refers to an impurity that is present in the proposed generic synthetic peptide, but not in the RLD.

[6] For definitions of specified and unspecified impurities, see guidances for industry *ANDAs: Impurities in Drug Substances* and *ANDAs: Impurities in Drug Products*, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidances *Impurities in New Drug Substances* (ICH Q3A(R2)) and *Impurities in New Drug Products* (ICH Q3B(R2)). The guidances referenced in this document are available at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs . We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

II. BACKGROUND

FDA considers any alpha amino acid polymer composed of 40 or fewer amino acids to be a peptide, not a protein. Glucagon, liraglutide, nesiritide, teriparatide, and teduglutide are peptides. A peptide is regulated as a drug under the FD&C Act unless the peptide otherwise meets the statutory definition of a "biological product" (e.g., a peptide vaccine) and is therefore regulated under the Public Health Service Act.[7]

In order for FDA to approve an ANDA, an applicant must demonstrate, among other things, that the proposed generic drug[8] has the "same" active ingredient(s), conditions of use, dosage form, route of administration, strength, and (with certain permissible differences) labeling as the RLD, and is bioequivalent to its RLD.[9] Additionally, FDA must find that the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the generic drug are adequate to assure and preserve its identity, strength, quality, and purity.[10] FDA approval of an ANDA reflects an Agency determination that the proposed generic drug is therapeutically equivalent to its RLD.[11]

In the past, analytical methods have not always been capable of adequately characterizing peptide products for submission in an ANDA. However, given the current state of technology for peptide synthesis and characterization (e.g., advances in high resolution mass spectrometry, liquid chromatography, high-resolution multi-dimensional NMR), FDA now believes it is possible for an ANDA applicant to demonstrate that the active ingredient in a proposed generic

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[7] For more information about terminology and regulatory authorities applied to amino acid polymers, see FDA's final rule, "Definition of the Term 'Biological Product'" (85 FR 10057, February 21, 2020). This final rule amends FDA's regulation that defines "biological product" to incorporate changes made by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) and the Further Consolidated Appropriations Act, 2020, and provides FDA's interpretation of the statutory term "protein." FDA interprets the statutory definition of "biological product" in section 351 of the Public Health Service Act such that any alpha amino acid polymer composed of 40 or fewer amino acids (i.e., a "peptide") is outside the scope of the term "protein."

[8] Throughout this guidance we use the term *generic drug* to refer to a new drug product described in an ANDA submitted under section 505(j) of the FD&C Act.

[9] See section 505(j)(2)(A) of the FD&C Act. An applicant may submit a petition seeking permission to submit an ANDA for a change in route of administration, dosage form, strength, or one active ingredient in a fixed combination drug product. See 21 CFR 314.93.

[10] Section 505(j)(4) of the FD&C Act.

[11] *Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling (21 CFR 314.3(b)). *Pharmaceutical equivalents* are drug products in identical dosage forms and route(s) of administr(ation that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rate. *Id*.

synthetic peptide is the same as the active ingredient in the RLD that is of rDNA origin, and demonstrate that such products are pharmaceutical equivalents.

All ANDAs must contain a description of the composition, manufacture, and specifications of the drug substance and the drug product.[12] An ANDA applicant is required to submit a full description of the drug substance including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; and the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance.[13] To ensure purity, applicants should propose and justify appropriate limits on the impurities in their drug substances and drug product.[14]

In reviewing an ANDA, FDA considers the types and amounts of impurities present in a proposed generic drug in comparison to its RLD.[15] While certain differences in impurity profiles between a proposed generic drug and the RLD may be permissible, FDA evaluates whether a generic drug contains impurities at levels greater than those found in the RLD and whether the impurities, including new impurities, are otherwise justified to help ensure, among other things, that the generic drug does not pose a greater safety risk than the RLD.

Whether a peptide is produced by a recombinant or synthetic process, impurities may result from the insertion, deletion, or modification of amino acid sequences or residues. These impurities can be controlled in the synthetic process. At low levels, consistent with batch-to-batch variability, they generally pose minimal pharmacological or toxicological risks that would affect safety or effectiveness. However, in some circumstances, peptide-related impurities may create the potential for differences in immunogenicity or may otherwise affect the safety or effectiveness of a peptide drug product. Because of these concerns about the potential for immunogenicity for glucagon, liraglutide, nesiritide, teriparatide, and teduglutide, the type of application that should be submitted for a proposed synthetic peptide that refers to a peptide of rDNA origin depends largely on the type of data that would be necessary to evaluate the differences in impurities between the proposed product and the previously approved product.

The recommendations for submission of an ANDA for the peptides covered by this guidance are designed primarily to help ensure that there is adequate information to assess the impurity profile

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[12] 21 CFR 314.94(a)(9) and 314.50(d)(1).
[13] 21 CFR 314.94(a)(9)(i) and 314.50(d)(1)(i).
[14] FDA may refuse to receive an ANDA that is incomplete because it does not on its face contain information required under section 505(j) of the FD&C Act or 21 CFR 314.94, which includes a demonstration of the purity of the drug substance and drug product and information on the impurities and residues (21 CFR 314.101(d)(3) and 314.94(a)(9) (requiring an ANDA to contain the information required under 314.50(d)(1)). See also the guidance for industry *ANDA Submissions – Refuse to Receive for Lack of Proper Justification of Impurity Limits*.
[15] See, e.g., the guidances for industry: *ANDAs: Impurities in Drug Substances* and *ANDAs: Impurities in Drug Products*.

of the proposed generic product as compared to the RLD of rDNA origin, particularly with respect to the risk of immunogenicity due to peptide-related impurities.

III. SCIENTIFIC CONSIDERATIONS FOR ANDAS FOR PROPOSED GENERIC SYNTHETIC PEPTIDES

A. Active Ingredient Sameness

A crucial factor in determining whether an ANDA meets the statutory requirements for approval is whether the active ingredient in the proposed generic drug is the "same" as that of the RLD.[16] The sameness of active ingredient in a proposed generic synthetic peptide can be established through physicochemical characterization, and biological evaluation such as comparative clinical pharmacokinetic (PK) and/or pharmacodynamic (PD) studies. Although compendial standards may be available for some peptides covered by this guidance, comparative testing of the proposed generic synthetic peptide and RLD product is recommended, as applicable.[17] ANDA applicants are encouraged to apply orthogonal analytical methods to characterize the following properties and other properties, as appropriate:

- Primary sequence and physicochemical properties
- Secondary structure
- Oligomer/aggregation states
- Biological activities (by in vitro or animal studies[18])

Where data demonstrate that the proposed synthetic peptide's active ingredient is the "same as" the active ingredient in the RLD, whether an application should be submitted as an ANDA or as an application submitted pursuant to section 505(b)(2) of the FD&C Act may depend on the proposed product's impurity profile, because differences in impurities may affect, among other things, the potential for immunogenicity.[19]

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[16] Section 505(j)(2)(A)(ii)(I) of the FD&C Act. *Active ingredient* is defined at 21 CFR 314.3(b).

[17] Because some properties, such as secondary structure, oligomer/aggregation states, and biological activity, may be affected by the formulation of the drug product, an applicant should compare and assess the formulation of the proposed generic and the RLD.

[18] FDA supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with the Office of Generic Drugs (OGD) (see section V below) if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. OGD will consider if such an alternative method could be assessed for equivalency to an animal test method.

[19] If an applicant has questions about submission of an application through the 505(b)(2) pathway, the applicant should contact the appropriate Office of New Drugs review division for assistance. For more information on contacting the appropriate Office of New Drugs review division for a possible 505(b)(2) application, see FDA's Enhanced Communication web page at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/enhanced-communication.

B. Impurities

In reviewing an ANDA, FDA considers the types and amounts of impurities present in a proposed generic drug in comparison to its RLD.[20] In general, a proposed generic synthetic peptide should not contain impurities at levels greater than those found in the RLD. Any impurities, including new impurities, should be justified to help ensure, among other things, that the generic drug does not pose a greater safety risk, including with respect to immunogenicity, than the RLD.

Regardless of whether a peptide drug product is produced by a recombinant or synthetic process, it may contain impurities resulting from degradation during product storage or from the method of producing the peptide. In general, impurities that result from degradation during storage of the product, rather than from how the peptide is produced, would be expected to be the same where the RLD and proposed generic synthetic peptide have the same active ingredient, generally the same inactive ingredients[21], and the same labeled storage conditions. FDA intends to generally consider the sameness of active ingredient, inactive ingredients, storage conditions, and impurities that result from degradation in its evaluation of an ANDA for a peptide drug product in the same manner it does for ANDAs for non-peptide drug products.

Impurities may also occur as a result of the specific process used to produce the peptide. The impurities produced by rDNA technology can be divided into three categories:

- Peptide-related impurities
- Host cell-related impurities
- Other (non-peptide-related) impurities

Peptide-related impurities include amino acid sequences related to, but different from, that of the active ingredient, as a result of insertion, deletion, or other modifications (e.g., oxidation or glycosylation) to the amino acid sequence, and residues of the peptide. Host cell-related impurities include host cell DNA and host cell proteins. Other impurities include residual

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[20] See, e.g., the guidances for industry *ANDAs: Impurities in Drug Substances* and *ANDAs: Impurities in Drug Products*.

[21] At present, approved drug products for the five peptides covered by this guidance are all intended for parenteral use. A parenteral drug product generally must contain the same inactive ingredients in the same concentration as the reference listed product, although an applicant may seek approval of a drug product that differs from the RLD in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product. See 21 CFR 314.94(a)(9)(iii); see also guidance for industry *ANDA Submissions—Refuse-to-Receive Standards*.

solvents, reagents, and metals.[22] Peptide-related impurities and other (non-host cell-related) impurities may result from the production of a peptide by both recombinant and synthetic processes. Host cell-related impurities, however, occur only in rDNA-origin peptide drug products.

Differences between the peptide-related impurities in a proposed generic synthetic peptide and those in an RLD of rDNA origin could produce different impurity profiles, which could adversely affect the safety or effectiveness of a proposed generic synthetic peptide product, if uncontrolled. The peptide-related impurity profiles for approved peptides of rDNA origin have been well characterized for the peptides covered by this guidance. Therefore, it may be feasible to compare the peptide-related impurity profile of the RLD to the peptide-related impurity profile of the proposed generic synthetic peptide. To enable such comparison, applicants should complete the following two actions:

1. Verify that for each peptide-related impurity found both in the proposed generic synthetic peptide and in the RLD, the level of this peptide-related impurity in the proposed generic synthetic peptide is not more than the level found in the RLD. Applicants may accomplish this verification by, for example, adjusting the synthetic route or purification strategies.

2. Identify and reduce or mitigate risks related to peptide-related impurities. Because of (1) the peptide-related impurities that could be present in the peptides covered by this guidance and (2) advances in analytical chemistry, synthetic peptide manufacturing and purification technology, and biological assays,[23] it would generally be appropriate for applicants to submit an ANDA for one of the peptides covered by this guidance if, among other things, for any new peptide-related impurity, the level for the proposed generic synthetic peptide is no more than 0.5 percent of the drug substance. A new peptide-related impurity level higher than 0.5 percent of the drug substance could raise concerns about the potential risk of immunogenicity; as a result, it may not be possible to adequately address the larger variance through the ANDA process (e.g., if the risk of immunogenicity requires a clinical investigation).

Accordingly, FDA believes that submitting an ANDA for one of the peptides covered by this guidance would be generally appropriate if, among other things, for any new specified peptide-

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[22] The ICH guidance *Q3C Impurities: Residual Solvents* recommends acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The ICH guidance *Q3D Elemental Impurities* presents a process to assess and control elemental impurities in the drug product using the principles of risk management described in ICH Q9. This process provides a platform for developing a risk-based control strategy to limit elemental impurities in the drug product.

[23] Because peptide-related and other impurities come from the starting materials, reagents, solvents, and the process used, an ANDA applicant should be able to determine what impurities might occur and could take steps (e.g., by following FDA and ICH guidances) to ensure that the impurity profile of a proposed synthetic peptide is acceptable.

related impurity, the level for the proposed generic synthetic peptide is no more than 0.5 percent of the drug substance.

A new specified peptide-related impurity level of no more than 0.5 percent of the drug substance for purposes of evaluating the appropriateness of submission as an ANDA is consistent with the small amount of unspecified peptide-related impurities observed in finished peptide drug products due to batch-to-batch variability, which occurs regardless of whether the peptide is produced by a recombinant or synthetic process. This flexibility is, however, subject to subsequent scientific review upon the submission of an ANDA and FDA may ask the ANDA applicant to further reduce the level of a specified peptide-related impurity depending on the risks associated with a particular impurity as well as with the proposed drug product.

For each new specified peptide-related impurity, the ANDA applicant should characterize the impurity. Further, the ANDA applicant should provide justification for why the presence of such impurity would not be expected to affect the safety of the proposed generic synthetic peptide or its effectiveness as compared to that of the RLD, including with respect to the risk of immunogenicity related to peptide-related impurities. This justification should take into consideration, among other things, the identity and amount of an impurity, the impurity's impact on the physicochemical and biological properties of the peptide, and the potential risks specific to the peptide.[24] The justification should include data showing that any differences in impurities between the proposed generic synthetic peptide and the RLD do not modify each of the following: the physicochemical properties, biological activity, or immunogenicity risk of the product. Such data should demonstrate for each new impurity that the impurity does not contain sequences that have an increased affinity for major histocompatibility complex (MHC), known as *T-cell epitopes.* Further, the data should demonstrate that the proposed generic synthetic peptide does not increase the aggregation propensity or the nature of the aggregates formed, especially under stress conditions, and does not contain impurities or contaminants that produce a greater or distinct stimulation of innate immune activity as compared to the RLD. Prospective ANDA applicants should contact the Office of Generic Drugs (OGD) if they have specific questions regarding what information should be provided.[25] Based on the information provided, FDA may recommend that additional non-clinical immunogenicity evaluations be completed for the proposed generic synthetic peptide.

[24] For example, where a peptide drug has a sequence identical to part of a human endogenous protein, and some function(s) of the protein is non-redundant, an immunogenic response that leads to antibodies directed against the endogenous protein could have far reaching consequences.

[25] See section V of this guidance for information about requesting assistance from OGD.

IV. SUBMISSION OF ANDAS FOR PROPOSED GENERIC SYNTHETIC PEPTIDES

The submission of an ANDA for a synthetic glucagon, liraglutide, nesiritide, teriparatide, or teduglutide drug product that references an approved peptide of rDNA origin would be generally appropriate if the statutory and regulatory requirements for an ANDA are met and, with respect to active ingredient sameness and peptide-related impurities:[26]

- The proposed generic synthetic peptide is characterized to show the sameness of the active ingredient to that of the RLD with respect to the following properties:
    - Primary sequence and physicochemical properties,
    - Secondary structure,
    - Oligomer/aggregation states, and
    - Biological activity/function (by in vitro or animal studies);

- For each peptide-related impurity that is found in both the proposed generic synthetic peptide and the RLD, the level of such impurity in the proposed product is the same as or lower than that found in the RLD;

- The proposed generic synthetic peptide does not contain any new specified peptide-related impurity (i.e., an impurity that is not also present in the RLD) that is more than the recommended threshold for a new peptide-related impurity (i.e., 0.5 percent of the drug substance);[27] and

- For any new specified peptide-related impurity that is no more than 0.5 percent of the drug substance, the applicant has characterized the impurity (e.g., the amino acid sequence and structure) and provided a justification for why, for each such impurity, the presence of such impurity would not be expected to affect the safety of the proposed generic synthetic peptide or its effectiveness as compared to that of the RLD, including with respect to the risk of immunogenicity.

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[26] Determinations as to whether FDA will receive for substantive review or approve an ANDA will be made subsequent to submission. Applicants are encouraged to review the following guidances for industry for more information: *ANDA Submissions – Content and Format of Abbreviated New Drug Applications*, *ANDA Submissions – Refuse-to-Receive Standards*, *ANDA Submissions – Refuse-to-Receive for Lack of Justification of Impurity Limits*, and *Immunogenicity Assessment for Therapeutic Protein Products* (which notes that "[a]lthough this guidance focuses on therapeutic protein products, the scientific principles may also apply to … peptides").

[27] If the proposed synthetic peptide product contains a new specified peptide-related impurity that is more than 0.5%, the applicant should consider following the procedures outlined in section V of this guidance for contacting the OGD to discuss a suitable pathway.

For such applications, FDA recommends that applicants apply sensitive and high resolution analytical procedures (e.g., UHPLC-HRMS)[28] to detect and characterize peptide-related impurities in a proposed generic synthetic peptide in comparison to the RLD. In general, for the peptides covered by this guidance, applicants should identify[29] each peptide-related impurity that is 0.10 percent of the drug substance or greater.[30] Depending on the potential immunogenicity risk of a particular product, applicants may be asked to also identify peptide-related impurities present at levels below this threshold.

Also for each new specified impurity, the applicant should provide justification, including data, to show that any differences in impurity profiles between the proposed generic synthetic peptide and the RLD do not modify each of the following: the physicochemical properties, biological activity, or immunogenicity risk of the product.[31] For example, such data should demonstrate that each new impurity does not contain sequences that have an increased affinity for MHC, known as T-cell epitopes, and that the proposed generic synthetic peptide does not alter the innate immune activity.

FDA may recommend conducting additional comparative studies that can be submitted under section 505(j) of the FD&C Act (e.g., in vitro, in vivo animal, clinical PK/PD equivalence), as appropriate, to assess whether a proposed generic synthetic peptide meets relevant approval standards, including that the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve its identity, strength, quality, and purity.

If it is necessary to conduct clinical studies to independently establish the safety or effectiveness of a proposed synthetic peptide, submission of an application under section 505(b) of the FD&C Act would be necessary. Once an application for a synthetic peptide product has been approved under section 505(c) of the FD&C Act, subsequent applications for that synthetic peptide product may be submitted as ANDAs.

V. REQUESTING ASSISTANCE FROM FDA

An applicant developing a proposed generic synthetic peptide for one of the peptides covered by this guidance may contact OGD to confirm whether the application may be submitted as an

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[28] See, e.g., Zeng K, et al., "Liquid Chromatography-High Resolution Mass Spectrometry for Peptide Drug Quality Control," AAPS J, 17(3), 643-51 (2015).

[29] For each peptide-related impurity that is 0.10%-0.5% of the drug substance, "identify" means characterize the structure of the peptide-related impurity.

[30] Identification of impurities that are 0.10% to 0.5% of the drug substance for proposed generic synthetic peptides supports FDA's assessment of the risk of immunogenicity.

[31] Appendix 1 illustrates FDA's recommendations for evaluating peptide-related impurities to determine whether submission of an ANDA for a synthetic peptide that references a peptide of rDNA origin is appropriate.

ANDA. An applicant may submit a controlled correspondence[32] to or request a pre-ANDA meeting with OGD. Controlled correspondence is appropriate if an applicant has a specific and targeted inquiry about the generic drug development process. The pre-ANDA meeting is appropriate for a prospective applicant seeking a dialogue with the Agency on a particular matter outside the scope of controlled correspondence. Requests for pre-ANDA meetings should be sent electronically through the CDER Direct NextGen Collaboration Portal.[33]

[32] See the guidance for industry *Controlled Correspondence Related to Generic Drug Development* for information on the types of inquiries accepted as controlled correspondence and submission of controlled correspondence to OGD.

[33] The CDER Direct NextGen Collaboration Portal may be accessed at https://edm.fda.gov/EDMIDPLogin/welcome?response_type=code&client_id=0oa1as7rb2poiYTch297&scope=openid%20profile&state=1802935594_1580919665259&redirect_uri=https%3A%2F%2Fedm.fda.gov%2Foidcclient%2Fedmrp.

APPENDIX 1 – RECOMMENDED EVALUATION OF PEPTIDE-RELATED IMPURITIES TO DETERMINE WHETHER SUBMISSION OF AN ANDA FOR A SYNTHETIC PEPTIDE THAT REFERENCES A PEPTIDE OF rDNA ORIGIN IS APPROPRIATE